

## **EDITORIAL COMMENTRY**

### **Backward in coming forward**

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As far back as the ancient Egyptians and Greeks, physicians have observed and interpreted the arterial pulse to help diagnose certain illnesses. However, until William Harvey's discoveries in the 17<sup>th</sup> century, some of the basic concepts were misunderstood. Harvey described the circular blood flow in the body and discovered that the arterial pulse is generated by the contraction of the left ventricle. He also came up with the concept that the arterial pulse is a wave, thus paving the way for modern studies in pulse wave analysis. Another pivotal discovery was the introduction of pulse wave velocity (PWV) by Crighton Bramwell in the early 20<sup>th</sup> century. He recognised that PWV changes in proportion to the arterial wall tension and blood pressure, and thus, is an indirect measure of arterial wall elasticity<sup>1</sup>. Despite these important historic discoveries, it has only been in the last 20 years, with advances in modern engineering, that the pulse wave analysis has become more widely available, reliable, and reproducible technique to assess arterial pulse waves.

It is now generally accepted that pulse wave reflections and arterial stiffness are important predictors of cardiovascular outcome. Adding value to information provided by traditional risk factors; improving risk classification, and predicting all-cause mortality<sup>2,3</sup>. However, the evidence concerning the relative value of more specific steady-state and pulsatile components of the pressure waveforms in mediating cardiovascular damage is conflicting<sup>4-7</sup>. The technique of wave separation analysis could potentially help in this respect, as it allows the pressure waves in the proximal aorta to be separated into forward and backward pressure waves. The forward wave is generated by the ventricular contraction, and its amplitude is determined by the compliance of the proximal aorta, and the ventricular contraction. The backward wave, also known as the reflected wave, is generated by the reflection of the forward wave from the peripheral arteries and hence, the amplitude of the reflected wave is

influenced by the characteristics of the peripheral vasculature, such as diameter and compliance, at the major sites of reflection<sup>8</sup>.

Data published in this issue of *American Journal of Hypertension* by Kolkenbeck-Ruh and colleagues explore the differential contributions of steady-state pressure and pulsatile pressure components to various measures of vascular end-organ damage (ventricular mass index (LVMI), carotid intima media thickness (cIMT) and aortic PWV) across the adult lifespan<sup>9</sup>. Their present data are taken from a relatively large population-based cross-sectional cohort of subjects recruited from families of black African descent in Johannesburg, South Africa. Detailed haemodynamic profiling was performed including assessment of the steady-state pressure (MAP) and pulsatile pressure components; forward (Pf) and backward pressure (Pb) waves. These were determined using SphygmoCor software v. 9.0, which separates the aortic waveform using a theoretical triangular flow wave. A novel aspect of the study is that the authors looked at the differential effects in subjects under 50 years of age versus those over 50 years of age, as well as looking at the specific contributions of pressure wave components to each vascular end-organ measure.

Kolkenbeck-Ruh *et al.* report that LVMI is associated with Pb in both young and old subjects. This association remained significant after adjusting for confounding factors, such as treatment for hypertension, smoking and lipid profiles<sup>9</sup>. These results confirm the findings by Chirinos *et al.* who showed that arterial wave reflections generally arrive at the central aorta in mid to late systole, thus increasing myocardial stress by increasing LV afterload and pressure in late systole<sup>10</sup>, and subsequently leading to an increase in LVM. In contrast, the data from Kolkenbeck-Ruh *et al.* demonstrate that the Pf was independently associated with cIMT, but only in older subjects. Notably, Pb was not associated with cIMT in either age

group. This suggests that cIMT is perhaps more influenced by the larger component of the pressure wave, Pf, and that changes in response to this cyclical stress occur over a longer time frame than LV mass does. It is perhaps surprising, given that Pf is influenced by aortic stiffness, that cIMT was not dependent on aortic PWV. This may be because Pf is a composite of stroke volume and stiffness i.e. a direct measure of stress. In support of the current data, findings by Boutouyrie *et al.* showed that carotid pulse pressure, often regarded as a surrogate of arterial stiffness, was a strong independent determinant of cIMT, whereas MAP and brachial pulse pressure were not. These findings suggest local pulsatile mechanical load contributes towards arterial remodelling<sup>11</sup>. Finally, Kolkenbeck-Ruh *et al.* show that both MAP and Pb are associated with aortic PWV in both age categories<sup>9</sup>. This seems logical, as PWV is mainly determined by the MAP at the time of measurement, whereas, wave reflections are determined by the properties of the peripheral arteries, such as stiffness. We previously demonstrated that an increased aortic PWV is associated with an increase in reflected wave amplitude and augmentation index<sup>12</sup>. This really highlights the key problem in trying to untangle the causality between, blood pressure, forward and backward travelling pressure waves, and stiffness of arteries; they are simply too closely connected with each other in complex multi-way pattern to draw conclusions.

Interestingly, the present study, and the recent large meta-analysis showing that African-Americans have increased arterial stiffness in comparison to white American<sup>13</sup>, may explain why individuals of black African descent are more sensitive to wave reflections than Caucasians, and subsequently, are more likely to develop LVH and heart failure, for a given blood pressure. The more general importance of pressure wave components is clearly highlighted by the fact that they predict cardiovascular mortality and events. The MESA study reported that Pb<sup>4</sup> and reflection magnitude<sup>6,7</sup>, which is a ratio of backward and forward

wave amplitude predicted cardiovascular (CV) events and mortality. Weber *et al.* showed, that Pb is the most consistent predictor of CV events and end-organ damage<sup>14</sup>. However, The Framingham Heart Study found that Pf, but not Pb or MAP was found to predicted CV outcome<sup>5</sup>.

What is the take-home message? The new data from Kolkenbeck-Ruh *et al.* suggest that there are differential associations between steady-state pressure, and aortic forward and backward travelling pressure waves, and measures of end-organ damage and that these associations are age-dependent<sup>9</sup>. Unfortunately, it is impossible to infer information about causality from this cross-sectional data, and therefore, it would be very interesting to see a large, long-term follow up study conducted which would track these changes throughout life. This would finally shed light to the causal roles steady-state and pulsatile pressure wave components in the development of high blood pressure, and vascular end-organ damage. Ultimately, if we understood the cause of the vascular end-organ damage, the treatment of hypertension could move forward and instead of dealing with damage, the cause could be treated in the early stage of the disease.

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## References

1. Ghasemzadeh N, Zafari AM. A Brief Journey into the History of the Arterial Pulse [Internet]. *Cardiol. Res. Pract.* 2011 [cited 2018 Nov 22]; Available from: <https://www.hindawi.com/journals/crp/2011/164832/>
2. Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, Boutouyrie P, Cameron J, Chen C-H, Cruickshank JK, Hwang S-J, Lakatta EG, Laurent S, Maldonado J, Mitchell GF, Najjar SS, Newman AB, Ohishi M, Pannier B, Pereira T, Vasan RS, Shokawa T, Sutton-Tyrell K, Verbeke F, Wang K-L, Webb DJ, Willum Hansen T, Zoungas S, McEniery CM, Cockcroft JR, Wilkinson IB. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. *J Am Coll Cardiol.* 2014;63:636–646.
3. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol.* 2010;55:1318–1327.
4. Wang K-L, Cheng H-M, Sung S-H, Chuang S-Y, Li C-H, Spurgeon HA, Ting C-T, Najjar SS, Lakatta EG, Yin FCP, Chou P, Chen C-H. Wave reflection and arterial stiffness in the prediction of 15-year all-cause and cardiovascular mortalities: a community-based study. *Hypertens Dallas Tex 1979.* 2010;55:799–805.
5. Cooper LL, Rong J, Benjamin EJ, Larson MG, Levy D, Vita JA, Hamburg NM, Vasan RS, Mitchell GF. Components of hemodynamic load and cardiovascular events: the Framingham Heart Study. *Circulation.* 2015;131:354–361; discussion 361.
6. Zamani Payman, Jacobs David R., Segers Patrick, Duprez Daniel A., Brumback Lyndia, Kronmal Richard A., Lilly Scott M., Townsend Raymond R., Budoff Matthew, Lima Joao A., Hannan Peter, Chirinos Julio A. Reflection Magnitude as a Predictor of Mortality. *Hypertension.* 2014;64:958–964.
7. Chirinos JA, Kips JG, Jacobs DR, Brumback L, Duprez DA, Kronmal R, Bluemke DA, Townsend RR, Vermeersch S, Segers P. Arterial Wave Reflections and Incident Cardiovascular Events and Heart Failure: The Multiethnic Study of Atherosclerosis. *J Am Coll Cardiol.* 2012;60:2170–2177.
8. Li Y, Gu H, Fok H, Alastruey J, Chowienczyk P. Forward and Backward Pressure Waveform Morphology in Hypertension. *Hypertens Dallas Tex 1979.* 2017;69:375–381.
9. Kolkenbeck-Ruh A, Motau TH, Naran R, Libhaber CD, Sareli P, Norton GR, Woodiwiss AJ. Organ-Specific, Age-Dependent Associations of Steady-State Pressures and Pulsatile Pressure Wave Components with End-Organ Measures. *Am J Hypertens.* 2018;
10. Chirinos JA, Segers P, Gupta AK, Swillens A, Rietzschel ER, De Buyzere ML, Kirkpatrick JN, Gillebert TC, Wang Y, Keane MG, Townsend R, Ferrari VA, Wiegers SE, St John Sutton M. Time-varying myocardial stress and systolic pressure-stress relationship: role in myocardial-arterial coupling in hypertension. *Circulation.* 2009;119:2798–2807.

11. Boutouyrie P, Bussy C, Lacolley P, Girerd X, Laloux B, Laurent S. Association between local pulse pressure, mean blood pressure, and large-artery remodeling. *Circulation*. 1999;100:1387–1393.
12. Hickson SS, Nichols WW, Yasmin null, McDonnell BJ, Cockcroft JR, Wilkinson IB, McEniery CM. Influence of the central-to-peripheral arterial stiffness gradient on the timing and amplitude of wave reflections. *Hypertens Res Off J Jpn Soc Hypertens*. 2016;39:723–729.
13. Buie JNJ, Stanley A, Nietert PJ, Logan A, Adams RJ, Magwood GS. Racial Disparities in Arterial Stiffness Between Healthy Whites and African Americans in the United States: A Meta-analysis. *J Natl Med Assoc* [Internet]. 2018 [cited 2018 Nov 29];Available from: <http://www.sciencedirect.com/science/article/pii/S0027968418301779>
14. Weber T, Auer J, O'Rourke MF, Kvas E, Lassnig E, Lamm G, Stark N, Rammer M, Eber B. Increased arterial wave reflections predict severe cardiovascular events in patients undergoing percutaneous coronary interventions. *EurHeart J*. 2005;26:2657–2663.